UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,292	05/09/2005	Karen Silence	A0848.70004US00	1144

23628 7590 05/29/2009

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
05/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,292	SILENCE ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,8,15,16,46,64 and 68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,8,15,46,64 and 68* is/are rejected.

7)☒ Claim(s) *16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received February 5, 2009 are acknowledged.

Claims 3, 4, 6, 7, 9-14, 17-45, and 47-63 have been canceled.
Claims 1, 2, 5, 8, 15, 16, 46, and 64 have been amended.
Claim 68 has been added.
Claims 1, 2, 5, 8, 15, 16, 46, 64, and 68 are pending in the instant application.

Specification

2. Applicant's amendments to title and abstract are acknowledged.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The rejection of claims 1, 2, 5, 8, 46, and 64 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement has been withdrawn in view of applicant's claim amendments received February 5, 2009 which have narrowed the scope of the claimed invention.

5. The rejection of claims 1, 2, 5, 8, 15, 46, and 64 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn in view of applicant's claim amendments received February 5, 2009 which have narrowed the breadth of the claimed invention.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. The rejection of claim 16 under 35 U.S.C. 112, second paragraph, has been obviated by applicant's amendment of said claim as part of the response received February 5, 2009.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. The rejection of claims 1, 2, 5, 8, 15, 46, and 64-67 under 35 U.S.C. 102(b) as being anticipated by Salfeld et al. (WO 97/29131) has been obviated by applicant's claim amendments received February 5, 2009.

Specifically applicant has canceled claims and has amended the remaining claims to recite biological sequence limitations not disclosed by Salfeld et al.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. The rejection of claims 1, 2, 5, 8, 15, 46, and 64-67 under 35 U.S.C. 103(a) as being unpatentable over Kink et al. (WO 99/64069, see entire document) in view of Muyldermans (US2007/0031424 A1, see entire document) has been obviated by applicant's claim amendments received February 5, 2009.

Specifically applicant has canceled claims and has amended the remaining claims to recite biological sequence limitations not disclosed by either Kink et al. or Muyldermans.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. The provisional rejection of claims 1, 2, 5, 8, 46, and 64 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20-

23, 26, and 28 of copending Application No. 10/553,105 has been withdrawn in view of applicant's claim amendments received February 5, 2009.

Specifically, the antibodies administered in the copending claims are specific for EGFR while the instant claims have been amended to recite administering antibodies that bind human TNFα.

14. Claims 1, 2, 5, 8, 15, 46, and 64 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 26, 28, 30, 34, 36 and 39 of copending Application No. 10/534,348. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims anticipate the instant invention. Specifically, the copending claims recite the oral administration of single domain antibodies that bind TNFα to patients for treatment of specific diseases such as Crohn's disease and ulcerative colitis. As such they are of narrower scope and thus anticipate the instant invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 1, 2, 5, 8, 15, 46, and 64 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13, 15 of copending Application No. 10/534,349. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims anticipate the instant invention. Specifically, the copending claims recite the oral administration of a composition comprising a single domain antibodies that binds TNFα and a single domain antibody that binds another target to patients in need thereof for treatment of inflammatory disorders. As such the copending claims are of narrower scope and thus anticipate the instant invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 1, 2, 5, 8, 15, 46, and 64 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20, 21, 23, 24, 44, 45, 47, 48 of copending Application No. 11/788,832 in view of Salfeld et al. (WO 97/29131). The copending claims recite the administration of single domain antibodies that bind TNFα for the treatment of various disorders such as Crohn's disease and ulcerative colitis. These claims differ from the instant invention in that they do not recite that the single domain antibodies are administered orally. Salfeld et al. disclose that single domain antibodies specific for TNFα are to be administered orally and thus the instant claimed invention would have been obvious to a person of ordinary skill in the art.

This is a provisional obviousness-type double patenting rejection.

17. Claims 1, 2, 5, 8, 15, 46, and 64 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 26, 50-59 and 61-67 of copending Application No. 11/636,300 in view of Salfeld et al. (WO 97/29131). The copending claims recite the administration of single domain antibodies that bind TNFα for the treatment of rheumatoid arthritis, an inflammatory disease. These claims differ from the instant invention in that they do not recite that the single domain antibodies are administered orally. Salfeld et al. disclose that single domain antibodies specific for TNFα are to be administered orally and thus the instant claimed invention would have been obvious to a person of ordinary skill in the art.

This is a provisional obviousness-type double patenting rejection.

Applicant has acknowledged the provisional obviousness type double patenting rejections concerning applications 10/534,348, 10/534,349, 11/636,300, and 11/788,832 and has requested that the rejections be held in abeyance until the indication of otherwise allowable subject material, at which time applicant may choose to file a terminal disclaimed.

Since the 10/534,348, 10/534,349, 11/636,300, and 11/788,832 applications have not been abandoned or had their claims amended such that they no longer read on the administration of single domain anti-TNFα antibodies and since no terminal disclaimers have been filed, the provisional rejections have been maintained.

18. The following are new grounds of rejection necessitated by applicant's claim amendments received February 5, 2009.

19. Claims 1, 2, 5, 8, 15, 46, 64, and 68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has claimed broad methods of treating human disorders by administering a single domain antibody which binds TNFα. Dependent claim 15 indicates that the "disorder" is inflammation, a broad process present in may "disorders" that is reasonably correlated with TNFα expression, and TNFα inhibitors are known to be effective in many disease settings, such as ulcerative colitis and rheumatoid arthritis. However, the claims are not limited to inflammation, or even to disorders that are TNFα -mediated, but rather read upon any and all disorders that may afflict a human subject. Such a scope is not reasonable for the reasons discussed more fully as part of the office action mailed August 5, 2008. Amending the independent claim to recite the limitations of claim 15, or limiting the disorders to TNFα -mediated disorders, if support for such language can be found in the specification as originally filed, would be beneficial in obviating this part of the rejection.

The independent claim also recites that the antibody that is administered to treat a "disorder" is a single domain antibody that comprises the CDR3 sequence of either SEQ ID NO:12 or SEQ ID NO:13. These sequences were isolated from an immunized llama as described in example 4 of the instant specification. It should be noted that

SEQ ID NOs:12 and 13 are full length VHH, and that SEQ ID NO:14 is a bivalent construct comprising two copies of SEQ ID NO:13 joined by a linker polypeptide. The specification discloses that SEQ ID NO:14 was therapeutically effective in a mouse colitis model (see example 7 beginning on page 62). As such it appears reasonable that the full length VHH isolated by applicant, as well as constructs comprising a full length VHH can be used in methods of treating TNFα -mediated diseases such as chronic colitis. However, the claims are not limited to administering a full length VHH which comprises the three CDR regions of SEQ ID NO12 or SEQ ID NO:13, but rather read on the administration of fragments of VHH, the smallest of which are peptides that consist of the CDR3 of either SEQ ID NO:12 or SEQ ID NO:13.

It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., see particularly 3:7-3:11). It is also known that single amino acid changes in a CDR can abrogate the antigen binding function of an antibody (Rudikoff et al., see entire document, particularly the abstract and the middle of the left column of page 1982).

However, the antibodies administered as part of the claimed invention are single domain antibodies, and as such they lack a light chain and it's associated three CDRs. To make up for the lack of a light chain, VHH such as those isolated by applicant, comprise longer CDR1 and CDR3 regions that adopt conformations that are not observed in typical V_H-V_L domains (Muyldermans et al., Trends Biochem Sci. 2001, see entire document, particularly page 234). Further, many VHH comprise distinct structural features in the framework regions, as well as a disulfide bond that joins CDR1 and CDR3 (Muyldermans S., J Biotechnol. 2001, see entire document, particularly page 281 and Figure 2). Also, it is not always CDR3 that is the most important CDR for antigen

binding, in that VHH in which the contribution of CDR1 is twice that of CDR3 for antigen binding are known (ibid. page 295 and Table 2). Thus, the breadth of the claimed invention reads on administering a peptide that consists of the CDR3 of SEQ ID NO:12 or SEQ ID NO:13 without any flanking sequence yet there is no data presented in the specification to demonstrate that such a peptide actually binds TNFα. It is noted that example 24 on page 75 discloses primers that could be used to make such a peptide, but it does not appear that such a peptide was actually made and tested for its ability to bind TNFα, either in vivo or in vitro.

The antibodies used in the instant claimed methods must not only be able to bind TNFα but they must also be effective in treating a "disorder". The art indicates that even VHH which are known to bind effectively in vitro do not necessarily work when administered in an in vivo setting (Harmsen et al., see entire document, particularly the abstract). The question of efficacy is compounded by the breadth of the claims, since it is known that antibody fragments typically have lower binding affinity and decreased half-life as compared with whole antibody, and indeed VHH are cleared more rapidly than scFV from the circulation (Muyldermans J Biotechnol., page 279). It should be noted that the mouse colitis model of example 7 used SEQ ID NO:14, a molecule which comprises two identical antigen binding sites which serve to increase the avidity of the interaction with antigen. Given that the contribution of CDR3 to the binding of TNFα is not disclosed for SEQ ID NOs:12 or 13, the fact that the claims read upon the administration of just a CDR3 peptide, and the fact that SEQ ID NO:14 was used for in vivo experiments and is reasonably expected to be a better binder than just an isolated CDR3 peptide because a) it has two antigen binding sites and b) the antigen binding sites comprise all three CDR and thus are reasonably expected to demonstrate a higher affinity for antigen as compared to an isolated CDR3 peptide, it is not clear that an isolated CDR3 peptide would be therapeutically effective, especially given that in vitro binding is not correlated with in vivo efficacy as evidenced by Harmsen et al.

Therefore, given the breadth of the claims, the amount of guidance and direction in the instant specification, and the teachings of the art, a skilled artisan would be

unable to practice full breadth of the instant claimed methods without performing additional, unpredictable research.

20. Claims 1, 2, 5, 8, 15, 46, 64, and 68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has claimed broad methods which recite the administration of a single domain antibody that binds TNFα and comprises the CDR3 sequence of either SEQ ID NOs:12 or 13. SEQ ID NOs: 12 and 13 are full length VHH that have been isolated from an immunized animal as per example 4. The specification discloses that the CDR3 of VHH#3E (a.k.a. SEQ ID NO:12) was cloned into an expression vector via PCR, but no data is provided concerning the binding of this isolated CDR3 peptide to TNFα, either in vivo or in vitro.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001, see especially page 1106 column 3).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court noted: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves

that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

As discussed above, the minimum structure for the antibody that is administered as part of the claimed method is a peptide that consists of the CDR3 sequence of either SEQ ID NO:12 or SEQ ID NO:13. In order to be effective in the claimed methods, the administered antibody must be able to bind TNFα. No data is provided which indicates that the CDR3 sequence of either SEQ ID NO:12 or SEQ ID NO:13 bind TNFα in the absence of additional sequence. As such, the specification does not disclose data to correlate the recited structure (CDR3 in the absence of additional sequence) with the recited function (binding TNFα).

Therefore, it appears that the broad genus of single domain antibodies recited for use in the methods claimed by applicant lacks adequate written description because there does not appear to be correlation between structure and function excepting the use of the full length polypeptides of SEQ ID NOs:12-14. As such, a skilled artisan would reasonably conclude that applicant was not in possession of the recited genus of single domain antibodies, and therefore was not in possession of methods of treating disorders by administering said antibodies.

Claim Objections

21. Claim 16 is objected to as being dependent upon a rejected independent claim, but would be allowable if rewritten in independent form including all of the limitations of the independent claim and any intervening claims.

22. No claims are allowable.

23. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Primary Examiner
Art Unit 1644

/Michael Szperka/
Primary Examiner, Art Unit 1644